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EXAMINER

RAGHU, GANAPATHIRAM

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/539,725	Applicant(s) RESKI ET AL.	
	Examiner GANAPATHIRAMA RAGHU	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38-67 and 71-80 is/are pending in the application.
- 4a) Of the above claim(s) 51-67, 69-77, 79 and 80 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38-50 and 78 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>03/31/06</u> . | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

Claims 38-67 and 69-80 are pending in this application for examination. Claims 38-50 and 78 are now under consideration. Claims 51-67, 69-77, 79 and 80 are withdrawn as they are drawn to non-elected invention.

Election/Restrictions

Applicants' election of Group I, claims 38-50 and 72 and as a species VEGF with traverse for prosecution in the reply filed on 12/31/07 is acknowledged. The traversal is on the grounds that the unity of invention exists between the restricted groups and all the claims are closely related and examination of all the claims will not pose a serious search burden.

Applicants arguments that the claims of Groups I-III have commonality of subject matter, a product i.e., transformed bryophyte cell (Group I), a method specifically making the product (Group II) and a means of carrying out the method i.e., vectors (Group III) and hence restriction between Groups I-III should be withdrawn or alternatively Groups I and II or Groups I and III should be rejoined are answered as follows.

Applicant's argument of the claims of Groups I-III are related as a product (Group I), a process of specifically making the product (Group II) and a means of carrying out the method (Group III) and the request for examination of all the claims are not deemed persuasive to withdraw the restriction requirement previously applied for the reasons stated below.

Claims as written are directed to a genus of modified bryophyte cells (in fact bryophyte (moss) is a Division comprising a vast majority of organisms), said bryophyte cells comprising modifications to a genus of structurally undefined genes (diverse members of bryophyte may have diverse structures for genes associated with fucosyl transferase and xylosyl transferase

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functions or may not have said gene structures and associated functions or may have other redundant mechanisms for encoding said polypeptides) that are rendered dysfunctional and further said transformed cell comprises a genus of mammalian galactosyl transferases with no structural limitations capable of producing any glycosylated polypeptide with any mammalian glycosylation pattern. Thus it becomes clear that a search of products, method of making the product and the means of making the product would involve text search of all the claimed bryophytes, enzymes and encoding structures and would impose a serious search burden. The search for each of these distinct groups would be overlapping but it would not be coextensive and this is supported by applicants admission that Groups I-III are patentably distinct (page 19 of the response), as the claims have to be evaluated for enablement, written description and other issues. When claims are given the reasonable broadest interpretation, the search would encompass a) diverse bryophytes and its modifications and b) said bryophyte further transformed with functionally diverse galactosyltransferases accompanied by diverse structures, and therefore, a separate search for each of the bryophyte and its modifications would be required in the patent and non-patent literature and analysis of results and this would be burdensome. Furthermore, group III claims (claims 67-77) are directed to a set of nucleic acid constructs and vectors and each vector comprises one gene of interest for transforming a bryophyte and therefore does not share the same special technical feature as required in group I i.e., a double knockout bryophyte cell and therefore the reference of Schafer et al., is relevant as said reference teaches transformed bryophyte cell and nucleic acid vector suitable for producing a transformed bryophyte cell with the gene of interest and additionally the method steps of group II (claims 51-

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66 and 79) as written do not lead to a bryophyte cell having a dysfunctional fucosyl transferase and a dysfunctional xylosyl transferase.

Please note that even if the International Authority found unity of invention regarding the instant claims, according to 37 CFR 1.499, if the Examiner finds that the national stage application lacks unity of invention under 37 CFR 1.475, the Examiner may in an Office Action require the applicant in the response to that action to elect an invention to which the claims shall be restricted. Such requirement may be made before any action at the discretion of the Examiner. Thus a finding of unity of invention in the international stage is not binding on the examination during national phase examination.

Therefore, for the above cited reasons searching of all claims is a serious search burden and contrary to applicant's argument, the requirement is still deemed proper and is therefore made FINAL.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). This application is a 371 of PCT/EP03/14576 filed on 12/18/2003 and claims priority to foreign application EPO 02028536.7 filed on 12/20/2002 and EPO 03022453.9 filed on 10/07/2003. A certified copy of the English translation of said foreign priority document has been provided dated 06/20/2005.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 03/31/2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS is considered by the examiner.

Objections to Abstract

The Abstract of the disclosure is objected to because, Abstract should be on a separate sheet of paper. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 45-47 are objected to, due to the following informality: Claims 45-47 recite the term “Physcomitrella...”. According to binomial nomenclature convention, species name should be in italics and examiner suggests amending the claim to recite “*Physcomitrella*...”. Appropriate correction is required.

Claim 50 is objected, due to the following informality: Claim 50 contains abbreviation VEGF in the claim. Examiner suggests at least in the first recitation of the abbreviations, expanding them to recite the full forms of what the abbreviation stands for. Appropriate correction is required.

Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 and claims 39-50 and 78 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 38 recites the phrase “i) a dysfunctional fucosyl transferase nucleotide sequence and ii) a dysfunctional xylosyl transferase nucleotide sequence. It is unclear to the examiner as to what makes a nucleic acid sequence which is incapable of encoding an active fucosyl transferase or xylosyl transferase a “dysfunctional fucosyl transferase gene or a dysfunctional xylosyl transferase gene”, one cannot define something by saying what it lacks. Clarification and correction is required.

Claims 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 40 recites the phrase “animal glycosylation patterns” and Claim 41 recites the phrase “mammalian glycosylation patterns”. It is unclear to the examiner as to what biological or chemical or physical characteristics define an “animal glycosylation pattern” or “mammalian glycosylation pattern”. Furthermore it is unclear what structural limitations the claimed bryophyte cell must have to be encompassed within the scope of these limitations. Clarification and correction required.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 50 recites the broad

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recitation “interferons” and “enzymes”, and the claim also recites “such as” which is the narrower statement of the range/limitation; “fertility hormones” and “growth factors” and also recites “including” which is the narrower statement of the range/limitation.

Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 38-50 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific bryophyte *Physcomitrella patens* wherein in said *Physcomitrella patens* the endogenous gene encoding for alpha 1, 3-fucosyltransferase (FucT) or an endogenous gene encoding for beta 1,2 xylosyltransferase (XylT) or both FucT and XylT has been disrupted through targeted insertion, disrupting the coding regions of said genes, further in said single knockout or double knockout *Physcomitrella patens* the gene encoding the human beta-1,4-galactosyltransferase catalyzing the following glycosylation pattern; UDP-galactose + N-acetyl-D-glucosaminylglycopeptide \rightleftharpoons UDP + beta-D-galactosyl 1, 4,-N-acetyl-beta-D-glucosaminylglycopeptide (GalT, GenBank X55415) has been integrated by homologous recombination and said *Physcomitrella patens* comprising said gene knockout (FucT and XylT or double knockout) and expressing the human galT is transformed with an expression construct encoding the secretable/soluble form of human vascular endothelial growth factor (VEGF), the specification does not reasonably provide enablement for **a)** any transformed bryophyte, **b)** wherein said bryophytes comprise a dysfunctional (impaired) FucT and XylT and **c)** said bryophytes comprising and encoding any galactosyltransferase from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation

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pattern. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 38-50 and 78, broadly encompass: **a)** any transformed bryophyte, **b)** wherein said bryophytes comprise a dysfunctional (impaired) FucT and XylT and **c)** said bryophytes comprising and encoding any galactosyltransferase from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation pattern. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of bryophytes and comprising a dysfunctional FucT or XylT (bryophytes are moss and belong to a Division comprising a vast number of organisms), extremely large number polynucleotide and encoding polypeptides and said polypeptides able to catalyze any mammalian glycosylation patterns in any glycopeptide as broadly encompassed by the claims.

In this case the disclosure is limited to a specific bryophyte *Physcomitrella patens* wherein in said *Physcomitrella patens* the endogenous gene encoding for alpha 1, 3-fucosyltransferase (FucT) or an endogenous gene encoding for beta 1,2 xylosyltransferase

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(XylT) or both FucT and XylT has been disrupted through targeted insertion, disrupting the coding regions of said genes, further in said single knockout or double knockout *Physcomitrella patens* the gene encoding the human beta-1,4-galactosyltransferase catalyzing the following glycosylation pattern; $\text{UDP-galactose} + \text{N-acetyl-D-glucosaminylglycopeptide} \rightleftharpoons \text{UDP} + \text{beta-D-galactosyl 1, 4,-N-acetylbeta-D-glucosaminylglycopeptide}$ (GalT, GenBank X55415) has been integrated by homologous recombination and said *Physcomitrella patens* comprising said gene knockout (FucT and XylT or double knockout) and expressing the human galT is transformed with an expression construct encoding the secretable/soluble form of human vascular endothelial growth factor (VEGF). This guidance provided is insufficient, as the breadth and scope of the bryophyte cells comprising modifications to a genus of structurally undefined genes (diverse members of bryophyte may have diverse structures for genes associated with fucosyl transferase and xylosyl transferase functions or may not have said gene structures and associated functions or may have redundant mechanisms) that are rendered dysfunctional and further said transformed cell comprises a genus of mammalian galactosyl transferases capable of producing any glycosylated polypeptide with any mammalian glycosylation pattern. Even the applicants in the specification on page 6, lines 10-15 have admitted that N-glycosylation is very complex and well regulated as N-glycosylation depends not only on developmental stages for plants but also dependent upon culture conditions. Therefore a skilled artisan requires the information regarding the gene structure, organization and its regulatory elements of all endogenous genes encoding the polypeptides involved in N-glycan synthesis of all bryophytes and amenable for rendering said genes dysfunctional without affecting the viability of the modified/transformed plants and the methods for transformation. In addition, any given galactosyltransferase activity (said bryophytes

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expressing a galactosyltransferase for the production of heterologous glycosylated polypeptides) is specific and limited to certain specific substrate(s) and its spectrum of activity is also limited and specific. In view of the breadth of the claims, the amount of experimentation required, the lack of guidance, working examples, and unpredictability of the art in predicting which of the many bryophytes are amenable for said transformations, practicing the claimed invention would require undue experimentation. As such, the specification fails to enable the entire scope of the claimed invention.

The specification does not support the broad scope of the claims because the specification does not establish: **(A)** diverse members of bryophyte and the diverse structures for genes associated with fucosyl transferase (FucT) and xylosyl transferase functions (XylT); **(B)** the structure of all the polypeptides and the encoding polynucleotides with the desired mammalian galactosyltransferase activity including variants, mutants and recombinants yielding desirable glycosylation patterns in said transformed bryophytes; **(C)** regions of the protein/polynucleotide structure which may be modified without affecting the activity of said polypeptides in case of mammalian galactosyltransferases or the viability of a bryophyte following rendering an endogenous gene encoding for FucT or XylT dysfunctional; **(C)** the general tolerance of the polypeptide to modification and extent of such tolerance; **(D)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and **(E)** sufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the

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claims broadly including al bryophytes with an enormous number of modifications and broadly able to yield any mammalian glycosylation pattern following transformation of said modified bryophytes with polynucleotides encoding desirable polypeptides that are to be glycosylated with the desired glycosylation pattern. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of: **a)** any transformed bryophyte, **b)** wherein said bryophytes comprise a dysfunctional FucT and XylT and **c)** said bryophytes comprising and encoding any galactosyltransferase from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation pattern (as in claims 38-50 and 78), is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 38-50 and 78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 38-50 and 78, as interpreted are directed to **a)** any transformed bryophyte, **b)** wherein said bryophytes comprise a dysfunctional (impaired) FucT and XylT and **c)** said bryophytes comprising and encoding any galactosyltransferase from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation pattern.

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In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, there are no structural limitations recited in claims with regard to: **I.** the members of the Division of bryophytes comprising a dysfunctional FucT or XylT or both **II.** said bryophytes comprising a genus of mammalian galactosyltransferases from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation pattern. While the specification in the instant application discloses a specific bryophyte *Physcomitrella patens* wherein in said *Physcomitrella patens* the endogenous gene encoding for alpha 1, 3-fucosyltransferase (FucT) or an endogenous gene encoding for beta 1,2 xylosyltransferase (XylT) or both FucT and XylT has been disrupted through targeted insertion, disrupting the coding regions of said genes, further in said single knockout or double knockout *Physcomitrella patens* the gene encoding the human beta-1,4-galactosyltransferase catalyzing the following glycosylation pattern; $\text{UDP-galactose} + \text{N-acetyl-D-glucosaminylglycopeptide} \rightleftharpoons \text{UDP} + \text{beta-D-galactosyl 1, 4,-N-acetyl-beta-D-glucosaminylglycopeptide}$ (GalT, GenBank X55415) has been integrated by homologous recombination and said *Physcomitrella patens* comprising said gene knockout (FucT and XylT or double knockout) and expressing the human galT is transformed with an expression construct encoding the secretable/soluble form of human

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vascular endothelial growth factor (VEGF) it fails to provide any information as to the a) structural features associated with any bryophyte encoding a FucT or XylT and that is amenable for rendering it dysfunctional or b) any galactosyltransferase from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation pattern. Due to the lack of description of any additional species/variants/mutants/recombinants from any source, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.

Patent Examiner

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Apr. 14, 2008.

/Rebecca E. Prouty/

Primary Examiner,

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